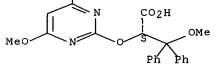
12-29-97

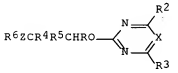
L7 ANSWER 1 OF 11 CAPLUS COPYRIGHT 1997 ACS
AN 1997:710122 CAPLUS
DN 127:344772
TI Structure and function of small arteries in salt-induced hypertension. Effects of chronic endothelin-subtype-A-receptor blockade
AU D'Uscio, Livius V.; Barton, Matthias; Shaw, Sidney; Moreau, Pierre; Luscher, Thomas F.
CS Division of Cardiology, Cardiovascular Research, University Hospital, Bern, Switz.
SO Hypertension (Dallas) (1997), 30(4), 905-911
CODEN: HPRTDN; ISSN: 0194-911X
PB American Heart Association
DT Journal
LA English
AB The involvement of endothelin in salt-induced hypertension is unclear. In the Dahl rat model, we studied the effects of a selective endothelin-subtype A (ETA) receptor antagonist, LU135252, on blood pressure, vascular structure, and function. Dahl salt-sensitive and salt-resistant rats were treated for 8 wk with 4% NaCl alone or in combination with LU135252 taken orally (60 mg/kg per day). The geometry and reactivity of basilar and mesenteric arteries were studied in vitro under perfused and pressurized conditions using a video dimension analyzer. Chronic salt administration increased systolic blood pressure by 37 mm Hg and media-lumen ratio of the basilar and mesenteric arteries in salt-sensitive rats. These structural changes were caused by eutrophic remodeling in basilar and hypertrophic remodeling in mesenteric arteries. Endothelium-dependent relaxations to acetylcholine and contractions to endothelin-1 were impaired in mesenteric arteries of salt-sensitive rats on a high NaCl diet. LU135252 prevented part of the increase in systolic blood pressure and structural and functional alterations but increased plasma endothelin 1 levels. LU135252 had no effect on these parameters in salt-resistant rats. These findings suggest that the long-term pressor effect of salt administration is mediated in part by the action of endogenous endothelin acting via ETA receptors. Thus, chronic ETA receptor blockade may be useful therapeutically to lower arterial pressure and prevent endothelial dysfunction and hypertrophic remodeling of resistance arteries in salt-sensitive forms of hypertension.
IT **171714-84-4**, LU 135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of chronic endothelin-subtype-A-receptor blockade on structure and function of small arteries in salt-induced hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, .alpha.-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-.beta.-methoxy-.beta.-phenyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 2 OF 11 CAPLUS COPYRIGHT 1997 ACS
AN 1997:700014 CAPLUS
DN 127:346410
TI Preparation of azinyloxypropionates as endothelin antagonists.
IN Riechers, Hartmut; Klinge, Dagmar; Amberg, Wilhelm; Kling, Andreas; Hillen, Heinz; Unger, Liliane; Elger, Bernd
PA BASF A.-G., Germany
SO Ger. Offen., 35 pp.
CODEN: GWXXBX
PI DE 19614534 A1 971016
AI DE 96-19614534 960412
DT Patent
LA German
OS MARPAT 127:346410
GI

date !

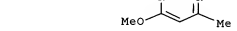


I

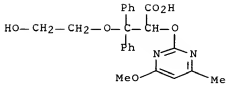
AB Title compds. [I; R = tetrazolyl, cyano, acyl; R2 = halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio; X = N, CR14; R14 = H, alkyl; R3 = R2, alkoxyamino; R3R14 = atoms to form a (substituted)(heterocyclic) ring; R4, R5 = (substituted) Ph, naphthyl; R6 = (substituted) alkyl, alkenyl, alkynyl; Z = O, S], were prepd. as endothelin antagonists (no data). Thus, Me 3,3-diphenyl-2,3-epoxypropionate, 2-hydroxyethyl acetate, and BF3.Et2O were stirred in Et2O at 0.degree. to room temp. to give Me 3-(2-acetoxyethoxy)-2-hydroxy-3,3-diphenylpropionate. The latter was heated with 2-methanesulfonyl-4-methoxy-6-methylpyrimidine and K2CO3 in DMF at 80.degree. to give 90% Me 3-(2-acetoxyethoxy)-2-(4-methoxy-6-methylpyrimidin-2-yloxy)-3,3-diphenylpropionate.

IT **198270-16-5P 198270-17-6P 198270-18-7P**
198270-19-8P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of azinyloxypropionates as endothelin antagonists)

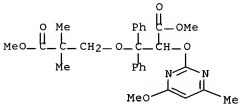
RN 198270-16-5 CAPLUS
CN Benzenepropanoic acid, .beta.-[2-(acetyloxy)ethoxy]-.alpha.-[(4-methoxy-6-methyl-2-pyrimidinyl)oxy]-.beta.-phenyl-, methyl ester (9CI) (CA INDEX NAME)



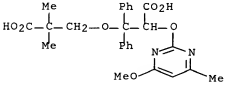
RN 198270-17-6 CAPLUS
CN Benzenepropanoic acid, .beta.-(2-hydroxyethoxy)-.alpha.-[(4-methoxy-6-methyl-2-pyrimidinyl)oxy]-.beta.-phenyl- (9CI) (CA INDEX NAME)



RN 198270-18-7 CAPLUS
CN Benzenepropanoic acid, .beta.-(3-methoxy-2,2-dimethyl-3-oxopropoxy)-.alpha.-[(4-methoxy-6-methyl-2-pyrimidinyl)oxy]-.beta.-phenyl-, methyl ester (9CI) (CA INDEX NAME)



RN 198270-19-8 CAPLUS
CN Benzenepropanoic acid, .beta.-(2-carboxy-2-methylpropoxy)-.alpha.-[(4-methoxy-6-methyl-2-pyrimidinyl)oxy]-.beta.-phenyl- (9CI) (CA INDEX NAME)



L7 ANSWER 3 OF 11 CAPLUS COPYRIGHT 1997 ACS
AN 1997:645657 CAPLUS
DN 127:314563
TI The orally active ETA receptor antagonist (+)-(S)-2-(4,6-dimethoxypyrimidin-2-yloxy)-3-methoxy-3,3-diphenyl propionic acid (LU 135252) prevents the development of pulmonary hypertension and endothelial metabolic dysfunction in monocrotaline-treated rats
AU Prie, Stephane; Leung, Tack Ki; Cernacek, Peter; Ryan, James W.; Dupuis, Jocelyn
CS Department of Medicine, Royal Victoria Hospital, Montreal, PQ, Can.
SO J. Pharmacol. Exp. Ther. (1997), 282(3), 1312-1318
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB Pulmonary hypertension is assocd. with endothelial dysfunction that may mediate or contribute to the disease process; among those abnormalities is an increase in circulating endothelin-1 levels. We investigated the effect of the orally active endothelin A receptor antagonist LU 135252 (LU) on the development of monocrotaline (MCT)-induced pulmonary hypertension and endothelial metabolic dysfunction. Rats were assigned to four groups by receiving a single dose of MCT or saline, followed by once-daily gavage with LU (50 mg/kg) or saline for 3 wk. Plasma immunoreactive endothelin-1

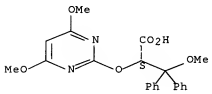
levels doubled after MCT and were unaffected by LU therapy. The MCT-induced increase in right ventricular systolic pressure (72.5 mmHg) and hypertrophy (right ventricle/[left ventricle plus septum wt.]; 0.58) were reduced by LU to 42.7 mmHg and 0.42, resp. LU, however, did not modify MCT-induced pulmonary artery medial hypertrophy. Pulmonary vascular endothelial metabolic activity was evaluated in isolated lungs by measuring endothelium-bound angiotensin-converting enzyme activity using a synthetic angiotensin-converting enzyme substrate, 3H-benzoyl-phenylalanyl-glycyl-proline. MCT reduced fractional 3H-benzoyl-phenylalanyl-glycyl-proline hydrolysis (0.488) which was normalized by LU therapy (0.563). LU treatment alone had no significant effect on any of these parameters. We conclude that the endothelin A antagonist LU reduces MCT-induced pulmonary hypertension and right ventricular hypertrophy and restores endothelial metabolic function. These results support the development of endothelin antagonists for the treatment of pulmonary hypertension and assocd. endothelial metabolic abnormalities.

IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ETA receptor antagonist LU 135252 prevents development of pulmonary hypertension and endothelial metabolic dysfunction in monocrotaline-treated rats)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, .alpha.-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-.beta.-methoxy-.beta.-phenyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 4 OF 11 CAPLUS COPYRIGHT 1997 ACS

AN 1997:459109 CAPLUS

DN 127:171298

TI Effect of chronic ETA-selective endothelin receptor antagonism on blood pressure in experimental and genetic hypertension in rats

AU Schiffrin, Ernesto L.; Turgeon, Andre; Deng, Li Y.

CS MRC Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, University of Montreal, Montreal, PQ, H2W 1R7, Can.

SO Br. J. Pharmacol. (1997), 121(5), 935-940
CODEN: BJPCBM; ISSN: 0007-1188

PB Stockton

DT Journal

LA English

AB Chronic treatment with a combined ETA/ETB endothelin receptor

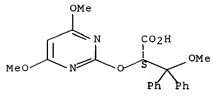
antagonist has been shown to reduce blood pressure in exptl. rat models of hypertension in which endothelin-1 gene overexpression occurs in the walls of blood vessels, particularly small, resistance-sized arteries, but not in those genetic or exptl. models of hypertension in which there is no overexpression of vascular endothelin-1. Failure of some exptl. models of hypertension to respond to treatment with the combined ETA/ETB endothelin antagonist may be due in part to blockade of vasorelaxant endothelial ETB receptors which could in theory reduce the efficacy of endothelin antagonism. In this study the orally active ETA-selective endothelin antagonists A-127722.5 and LU 135252 were used in chronic expts. on deoxycorticosterone acetate (DOCA)-salt hypertensive rats (which overexpress vascular endothelin-1 and respond with blood pressure lowering to combined ETA/ETB endothelin receptor antagonism), on spontaneously hypertensive rats (SHR) (which do not overexpress vascular endothelin-1 and do not respond with blood pressure lowering to the combined ETA/ETB receptor antagonist), and in 1-kidney 1 clip Goldblatt (1-K 1C) hypertensive rats (which present mild overexpression of vascular endothelin-1 but do not respond with blood pressure lowering to the combined ETA/ETB receptor antagonist). Addnl., it has been suggested that interruption of the renin-angiotensin system may sensitize responses to endothelin antagonism. Accordingly, SHR were treated with an angiotensin converting enzyme inhibitor, cilazapril, in addn. to the ETA receptor antagonist. Blood pressure of DOCA-salt hypertensive rats was lowered by a mean of 24 and of 27 mm Hg ($P<0.01$) by A-127722.5 after 4 wk of treatment, when given orally at two different doses (10 and 30 mg kg-1 day-1), and by 18 mm Hg by LU 135252 50 mg kg-1 day-1. SHR treated with A-127722.5 for 8 wk starting at 12 wk of age exhibited the same progressive rise in blood pressure as untreated SHR. Addn. of cilazapril resulted in similar redn. of blood pressure in A-127722.5-treated and untreated SHR. Treatment of 1-K 1C hypertensive rats with the dose of LU 135252 which lowered blood pressure in DOCA-salt hypertensive rats did not cause any redn. in blood pressure relative to untreated rats. These results demonstrate that treatment with either dose of the selective ETA receptor antagonists A-127722.5 or LU 135252 caused redns. in blood pressure similar to those obtained for a combined ETA/ETB endothelin antagonist. Blood pressure was lowered only in hypertensive rats known to overexpress vascular endothelin-1 (DOCA-salt hypertensive rats) but not in those which do not (SHR) or only have mild vascular overexpression of endothelin-1 gene (1-K 1C hypertensive rats). Redn. in activity of the renin-angiotensin system in SHR did not sensitize blood pressure to potential hypotensive effects of an ETA-selective receptor antagonist.

IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of chronic ETA-selective endothelin receptor antagonism on blood pressure in exptl. and genetic hypertension in rats)

RN 171714-84-4 CAPLUS

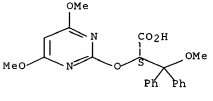
CN Benzenepropanoic acid, .alpha.-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-.beta.-methoxy-.beta.-phenyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 5 OF 11 CAPLUS COPYRIGHT 1997 ACS
AN 1997:402671 CAPLUS
DN 127:157209
TI Endothelin-1 mediates the development of severe acute pancreatitis
AU Foitzik, Thomas; Faulhaber, J.; Hotz, H. G.; Kirchengast, M.; Buhr, H. J.
CS Abteilung Allgemein-, Gefass- Thoraxchirurgie, Klinikum Benjamin Franklin, Berlin, D-12200, Germany
SO Chir. Forum Exp. Klin. Forsch. (1997) 749-753
CODEN: CFEKA7; ISSN: 0303-6227
PB Springer
DT Journal
LA German
AB In edematous pancreatitis of rats, endothelin-1 (ET-1) decreased pancreatic capillary blood flow and caused development of acinar cell necrosis. Transgenic rats with ET-1 receptor overexpression developed more severe disease, while prophylactic administration of the selective ET-1 receptor antagonist, LU 135252, ameloriated disease severity. After manifestation of necrotizing pancreatitis, ET-1 receptor blockade enhanced decreased pancreatic capillary blood flow and decreased mortality although the development of acinar cell necrosis was not diminished. Improved survival was assocd. with less ascites and decreased hematocrit indicating decreased fluid loss into the 3rd space and suggesting that the antagonist counteracted an ET-1-induced increase in vascular permeability.
IT **171714-84-4**, LU 135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-1 mediates the development of acute pancreatitis)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, .alpha.-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-.beta.-methoxy-.beta.-phenyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 6 OF 11 CAPLUS COPYRIGHT 1997 ACS
AN 1997:157448 CAPLUS
DN 126:195755
TI Effects of chronic ETA-receptor blockade in angiotensin II-induced hypertension
AU D'uscio, Livius V.; Moreau, Pierre; Shaw, Sidney; Takase, Hiroyuki; Barton, Matthias; Luscher, Thomas F.
CS Division of Cardiology, Cardiovascular Research, University Hospital, Bern, Switz.
SO Hypertension (Dallas) (1997), 29(1, Pt. 2), 435-441
CODEN: HPRTDN; ISSN: 0194-911X
PB American Heart Association
DT Journal
LA English
AB Angiotensin II, a constrictor and mitogen of vascular smooth muscle cells, affects the release of endothelium-derived factors such as nitric oxide or endothelin-1. This study investigated the influence of endothelin-1, using the selective endothelin A receptor antagonist LU 135252, on blood pressure and endothelial function in angiotensin II-induced hypertension in the rat. Two weeks of angiotensin II administration (200 ng/kg per min) increased systolic blood pressure (35 mm Hg; tail-cuff method) compared with placebo. LU 135252 alone did not affect systolic pressure but lowered the angiotensin II-induced pressure increase. In isolated aortic rings, endothelium-dependent relaxations to acetylcholine were reduced in the angiotensin II group (vs. placebo) and improved by concomitant chronic LU 135252 treatment (vs. angiotensin II). Blood pressure elevation strongly correlated with impaired endothelium-dependent relaxations to acetylcholine. LU 135252 did not affect endothelium-independent relaxations to sodium nitroprusside, which were diminished after angiotensin II treatment. In quiescent rings, chronic angiotensin II administration enhanced endothelium-dependent contractions to acetylcholine, which were reduced by LU 135252. Impaired contractions to endothelin-1 and norepinephrine in the angiotensin II group were normalized after treatment with LU 135252. Thus, chronic therapy with LU 135252 partially prevents angiotensin II-induced hypertension and the alterations of the endothelial function obsd. in this exptl. model.
IT **171714-84-4**, LU 135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of chronic ETA-receptor blockade in angiotensin II-induced hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, .alpha.-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-.beta.-methoxy-.beta.-phenyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

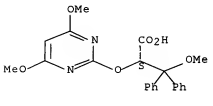
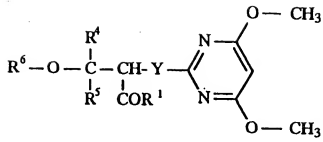


Tabelle 2



Nr.	R^6	R^4	R^5	Y	R^1	Diastereomere	Fp
2.1	Benzyl	Phenyl	Methyl	O	OCH_3	1:1	11
2.2	Benzyl	Phenyl	Methyl	O	OH	3:2	16
2.3	Benyzl	Phenyl	Methyl	S	OCH_3	1:1	
2.4	Benyzl	Phenyl	Methyl	S	OH		
2.5	Methyl	2-Fluorphenyl	Methyl	O	OCH_3	1:1	12
2.6	Methyl	2-Fluorphenyl	Methyl	O	OH		
2.7	Methyl	3-Methoxyphenyl	Methyl	O	OCH_3	1:0	13
2.8	Methyl	3-Methoxyphenyl	Methyl	O	OH	1:0	18
2.9	Methyl	4-i-Propylphenyl	Methyl	O	OCH_3		
2.10	Methyl	4-i-Propylphenyl	Methyl	O	OH		
2.11	Methyl	2-Methylphenyl	Methyl	O	OCH_3	3:1	12
2.12	Methyl	2-Methylphenyl	Methyl	O	OH	1:1	13
2.13	Methyl	3-Methylphenyl	Methyl	O	OCH_3		
2.14	Methyl	3-Methylphenyl	Methyl	O	OH		
2.15	Methyl	4-Methylphenyl	Methyl	O	OCH_3		
2.16	Methyl	4-Methylphenyl	Methyl	O	OH		
2.17	Methyl	4-Bromphenyl	Methyl	O	OCH_3		
2.18	Methyl	4-Bromphenyl	Methyl	O	OH		
2.19	Methyl	2-Furyl	Methyl	O	OCH_3		
2.20	Methyl	2-Furyl	Methyl	O	OH		
2.21	Methyl	3-Furyl	Methyl	O	OCH_3		
2.22	Methyl	3-Furyl	Methyl	O	OH		
2.23	Methyl	2-Thienyl	Methyl	O	OCH_3		
2.24	Methyl	2-Thienyl	Methyl	O	OH		
2.25	Methyl	2-Pyridyl	Methyl	O	OCH_3		
2.26	Methyl	2-Pyridyl	Methyl	O	OH		
2.27	Methyl	3-Pyridyl	Methyl	O	OCH_3		
2.28	Methyl	3-Pyridyl	Methyl	O	OH		
2.29	Methyl	4-Pyridyl	Methyl	O	OCH_3		
2.30	Methyl	4-Pyridyl	Methyl	O	OH		
2.31	Methyl	3-Chlorphenyl	Methyl	O	OCH_3		
2.32	Methyl	3-Chlorphenyl	Methyl	O	OH		
2.33	Methyl	2-Thiazolyl	Methyl	O	OCH_3		
2.34	Methyl	2-Thiazolyl	Methyl	O	OH		
2.35	Methyl	3-Isoxazolyl	Methyl	O	OCH_3		
2.36	Methyl	3-Isoxazolyl	Methyl	O	OH		
2.37	Methyl	4-Imidazolyl	Methyl	O	OCH_3		
2.38	Methyl	4-Imidazolyl	Methyl	O	OH		
2.39	Methyl	2-Pyrazolyl	Methyl	O	OCH_3		
2.40	Methyl	2-Pyrazolyl	Methyl	O	OH		